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Darunavir population pharmacokinetic model based on HIV outpatient data

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Conflicts of Interests

The authors declare that there are no conflicts of interests related to this study.

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Abstract

Introduction: Darunavir is a second-generation protease inhibitor and is registered for the treatment of human immunodeficiency virus (HIV) -1 infection. The aim of this study was to develop and validate a darunavir population pharmacokinetic model based on data from daily practice.

Methods: Datasets were obtained from two hospitals: ASST Fatebenefratelli Sacco University Hospital, Italy (hospital A) and University Medical Center Groningen, The Netherlands (hospital B). A pharmacokinetic model was developed using data from the largest dataset using the iterative two-stage Bayesian procedure within the MWPharm software package. External validation was conducted using data from the smaller dataset with Passing-Bablok regression and Bland-Altman analyses.

Results: In total, data from 198 patients from hospital A and 170 patients from hospital B were eligible for inclusion. A one-compartment model with first-order absorption and elimination resulted in the best model. The Passing-Bablok analysis demonstrated a linear correlation between measured concentration and predicted concentration with $r^2 = 0.97$ ($p < 0.05$). The predicted values correlated well with the measured values as determined by a Bland-Altman analysis and were overestimated by a mean value of 0.12 mg/L (range 0.23-0.94 mg/L). 98.2% of the predicted values were within the limits of agreement.

Conclusion: A robust population pharmacokinetic model was developed which can support therapeutic drug monitoring of darunavir in daily outpatient settings.

Keywords: Pharmacokinetics; antiretrovirals; HIV/AIDS; Therapeutic drug monitoring (TDM)

Background

Darunavir is a second generation protease inhibitor and is registered for the treatment of human immunodeficiency virus (HIV) -1 infection in therapy-naïve and therapy-experienced adults and paediatric patients aged ≥ 6 years.^{1, 2} Once-daily dosage of 800 mg darunavir is approved for use in treatment-naïve patients and a twice-daily dosage of 600 mg darunavir is approved for use in treatment-experienced patients.³ Darunavir is co-administered with 100 mg ritonavir or with 150 mg cobicistat in order to improve its exposure, as darunavir is almost exclusively metabolized by cytochrome P450 3A4.⁴⁻⁶ In healthy volunteers, darunavir exposure increased by 30% when ingested with food, irrespective of the type of food.⁷ For darunavir, a wide inter-patient pharmacokinetic variability has been observed.^{2, 8, 9} This pharmacokinetic variability can be attributed to treatment non-adherence, co-medication interactions, variability of cytochrome P450 3A4 iso-enzyme activity and patient demographics.^{2, 5, 8, 10} Pharmacokinetic variability may have detrimental effects by causing suboptimal darunavir concentrations and drug resistance resulting from the propagation of HIV-1 pseudo-species with protease mutations.¹¹ Therapeutic drug monitoring (TDM) potentially is a powerful tool to optimize treatment and to prevent drug resistance if a correlation exists between drug concentrations and (adverse) effects, if a drug has large inter-individual pharmacokinetic variability, or if a drug has a narrow therapeutic index.¹² For darunavir, a correlation exists between drug concentrations and effects^{1, 5} and therefore TDM has the potential to optimise efficacy in standard care. In Dutch daily practice, the trough concentration of darunavir is often used to help physicians determining the follow-up treatment with darunavir.¹³ In settings with adequate resources, TDM is commonly used in the

cases of: drug-drug interactions, renal or hepatic morbidity, pregnancy administration of drug doses not commonly used, virologic failure, suspicion of non-adherence, and adverse events.¹⁴ Collection of multiple plasma samples during one dosing interval to measure total drug exposure is time-consuming, expensive and burdensome to patients and to the health care system in a routine care setting. Furthermore, trough concentrations, the most frequently used pharmacokinetic parameter in TDM, is not always captured due to varying dosing schedules of patients in daily practice. A population pharmacokinetic model can provide a solution as it can be used to predict the (trough) plasma concentration profile of darunavir with a limited number of samples.^{2, 8} Two population pharmacokinetic models with different results were developed: one based on a one-compartment model² and one suggesting a two-compartment model.⁸ The aim of this study was to investigate which kind of model best describes the data from our outpatient setting by using the two previously published models prior to our own modelling experiment and to subsequently develop and validate a population pharmacokinetic model with data from daily practice, in order to predict darunavir trough levels in an HIV outpatient setting using user friendly software.

Materials and Methods

DATA COLLECTION

This study was conducted using two datasets from two hospitals: ASST Fatebenefratelli Sacco University Hospital, Milano, Italy (ASST) and the University Medical Center Groningen, The Netherlands (UMCG). All measured darunavir plasma concentrations were extracted from the ASST electronic patient database (April 2015 - August 2017) and from the UMCG electronic patient database (January 2010 - May 2017). Based on the size, the ASST dataset was named 'hospital A' and the UMCG dataset was named 'hospital B'. Approval by

the Ethics Committee was deemed unnecessary for ASST because, under Italian law, such an approval is required only for prospective clinical trials investigating medical products for clinical use. The ethical review board of the UMCG evaluated the study and waived the need for written informed consent due to the retrospective nature of the study (METc 2015.010). This was a retrospective data record review; the data were collected for clinical purposes and were anonymized for the study.

Data of patients ≥ 18 years of age and treated with darunavir were eligible for inclusion in this study. Both datasets were comprised of retrospectively collected data from HIV infected patients using darunavir/ritonavir 600/100 mg twice-daily or 800/100 mg once-daily. The following data were extracted from the medical records of the participants: sex, age, weight, height, serum creatinine concentration, darunavir dosage, time of darunavir intake, time of blood sampling and darunavir plasma concentration. The weight obtained during the outpatient visit of drug level measurement was documented in the research database; for serum creatinine concentration, the corresponding value during the visit of drug level measurement or within a period of ± 15 days was documented. Darunavir plasma concentrations were excluded if the time of drug intake or time of blood sampling was unknown and if the measured darunavir concentration was below the lower limit of quantification (< 0.2 mg/L for both hospitals). In cases where the height or weight of the patient were not documented, the average height (male: 1.80 m; female: 1.70 m) and weight (male: 80 kg; female 70 kg) according to the Dutch Central Bureau of Statistics (CBS) or average height (male: 1.75 m; female: 1.65 m) and weight (male: 75 kg; female: 65 kg) according to the Italian National Institute of Statistics (ISTAT) were inserted.^{15, 16} The addition of mean weight and height values for missing data was accepted up to 10% per dataset. In cases where the number of missing values exceeded 10%, the corresponding

patients were excluded. Darunavir plasma concentrations were analysed by a validated liquid chromatography-tandem mass spectrometry method.¹⁷

POPULATION PHARMACOKINETIC MODEL DEVELOPMENT

All pharmacokinetic calculations and modelling were performed using the MWPharm software package (version 3.82; Mediware, Zuidhorn, The Netherlands).¹⁸ The dataset with the largest population in terms of highest number of unique patients (hospital A) was chosen for pharmacokinetic model development and the dataset with the lower number of unique patients (hospital B) was used as the external validator set. The development dataset was imported in MWPharm to develop a population pharmacokinetic model using an iterative two-stage Bayesian (ITSB) procedure (the KinPop model of the MWPharm software package).¹⁹ The modelling was performed with the following estimated pharmacokinetic parameters: total body clearance (CL), volume of distribution (V) and oral absorption rate constant (K_a). CL was calculated using the equation: $CL = CL_m \times \left(\frac{BW}{70}\right) + f_r \times CL_{cr}$, where CL_m is metabolic clearance (in liters per hour per 70 kg body weight), BW is body weight (kilograms), f_r is the ratio of the renal clearance of darunavir and the creatinine clearance, CL_{cr} is the creatinine clearance calculated with the Chronic Kidney Disease Epidemiology collaboration (CKD-EPI) formula (converted to unit liter/hour) [20]. V was calculated using the equation: $V = V_1 \times LBM_c$, where V_1 is the volume of distribution (in liters per 70 kg LBMc) and LBMc is the lean body mass corrected, calculated with $LBM_c = LBM + (BW - LBM) \times f_d$, where LBM is calculated from $50.0 + 0.9 \times (\text{Height} - 152)$ for males and $45.5 + 0.9 \times (\text{Height} - 152)$ for females.²¹ Height is body height in cm, and f_d is a dimensionless parameter describing the degree of distribution into fatty tissue.²² For the two-compartment model, additional estimated pharmacokinetic parameters were:

intercompartmental clearance (CL_{12} , in liter per hour per 70 kg body weight) and volume of distribution of the peripheral compartment (V_2 , in liters per kg LBMc). Pharmacokinetic parameters were assumed to be log-normally distributed and the residual error was assumed to be normally distributed and equal to the standard deviation (SD) of the assay which was estimated as $0.2 + 0.05 \times C$, where C is the observed darunavir plasma concentration.

ITSB needed initial estimates for each population parameter (mean and standard deviation (SD)) to start the iterative process.¹⁹ In order to perform the ITSB procedure for the development of a one-compartment model with first-order elimination, initial population pharmacokinetic parameters from Arab-Alameddine et al. and darunavir Summary of Product Characteristics (SPC) were used^{2, 23} (supplement 1, <http://links.lww.com/TDM/A279>).

Subsequently, the development of a two-compartment model for darunavir was also explored based on initial pharmacokinetic data from Molto et al. and darunavir SPC^{8, 23} (supplement 1, <http://links.lww.com/TDM/A279>).

A stepwise approach was used to find a model that fitted the darunavir data best, comparing one- and two-compartment models. The goodness-of-fit of the newly designed population pharmacokinetic models were evaluated using the Akaike Information criterion (AIC).¹⁹ Selection of a one- or two-compartment model was based on (1) the lowest value of the AIC, and (2) the plausibility of the pharmacokinetic parameters. A drop in the AIC of 2 or more was considered to be the threshold for a better fitting model.²⁴ Furthermore, different values for f_d and f_r were inserted in order to observe the best fit based on AIC.

The KinPop module of the MWPharm software package has three settings for the inclusion of pharmacokinetic parameters in a model: by iterative two-stage Bayesian analysis (“Bayesian”), estimated with a predefined fixed population value (“fixed population

Bayesian”; FPB), or set to a fixed value (“fixed”). In the modelling procedure of the one-compartment model, the population pharmacokinetic parameters CL_m , V_1 and K_a were first set on fixed values. The same pharmacokinetic parameters were also set on fixed values for the modelling procedure of the two-compartment model in addition to CL_{12} and V_2 . The first step in developing the model was to set all parameters fixed to the literature values in supplement 1 and change one parameter at a time to either Bayesian or to the fixed value. The parameter with the lowest AIC was chosen for the next step. In step 2, the parameter with the lowest AIC was set to Bayesian and all other parameters were changed one by one to Bayesian. These steps were repeated in the next cycle using previous population parameters until the set with population parameters best fitting the data was found.

For the final parameter set, the nonparametric 95% confidence intervals of the population parameters and their inter-individual standard deviations were estimated by bootstrap analysis ($n=1,000$), which could be considered as a resampling technique for internal validation.

POPULATION PHARMACOKINETIC MODEL VALIDATION

External validation was performed by Bayesian fitting of the pharmacokinetic model to each individual in the validator dataset, using the previously developed model, as this provides the strongest evidence for model validation. The Kinpop module in MW\Pharm was used with one cycle set as a maximum. In this setting, the algorithm implemented in the MW\Pharm software determines the predictive power of a population pharmacokinetic model (a model's ability to predict serum levels of an individual patient), as opposed to the iterative procedure for the fitting of a new population pharmacokinetic model to population data. Passing-Bablok regression and Bland-Altman analyses were used to assess the agreement between the measured concentration and the predicted concentration.

For the bootstrap analysis and external validation, the final model was used, and if this model appeared to be inappropriate, the second-best logical model was also used for the bootstrap analysis and external validation.

P values of ≤ 0.05 were considered statistically significant. All statistical analyses were either performed as part of the MWPharm population analysis or computed using SPSS version 23 (IBM, Armonk, NY, USA).

Results

DATASET

198 unique patients with a total of 198 samples for hospital A and 170 unique patients with a total of 170 samples for hospital B were eligible for inclusion (supplement 2, <http://links.lww.com/TDM/A280>). The demographic characteristics of both patient populations were comparable (table 1). The percentage of missing values did not reach the threshold of 10% in both databases. No data was missing in the dataset of hospital A. In the dataset of hospital B, the weight of 14 participants (8.2%) and the height of 1 participant (0.6%) were not documented and therefore the average height and weight according to the CBS were used in these cases.

POPULATION PHARMACOKINETIC MODEL

The settings and results of the different one- and two-compartment submodels developed in order to find the model with the best goodness of fit are shown in supplement 3, <http://links.lww.com/TDM/A281>. Due to the absence of data on drug concentrations following parenteral darunavir administration as a comparison for oral administration to measure bioavailability, bioavailability was fixed in all parameterizations at the literature

value of 0.82.²³ A one-compartment model with a first-order absorption and elimination, a distribution to fatty tissue factor (f_d) of 5 and a f_r value of zero resulted in the best model. The addition of a second compartment did not significantly improve the fit based on AIC. In our dataset, the second compartment was estimated as 0.051 L/kg, which is negligible as a significant peripheral compartment.

The one-compartment model with only CL_m set on Bayesian (Model 1) had the lowest AIC value (945.31). This model implies that the volume of distribution (in L/kgLBMc) is the same for each patient, which does not seem logical. For that reason, the model with the second-best AIC value (Model 2) was also externally validated. This model had an AIC = 1584.89 with both CL_m and V_d set on Bayesian. The population pharmacokinetic model parameters of both models are shown in table 2. The modelling process of the different values for fat distribution (f_d) and the in- and exclusion of the f_r are shown in supplement 4, <http://links.lww.com/TDM/A282>.

EXTERNAL VALIDATION

For both models 1 and 2, an external validation was performed with the dataset from hospital B. The agreement between the measured concentration (C_{measured}) and the predicted concentration ($C_{\text{predicted}}$) was assessed in a Passing-Bablok analysis, shown in figure 1. The Passing-Bablok analysis demonstrated a positive linear correlation between C_{measured} and $C_{\text{predicted}}$ with $r^2 = 0.85$ ($P < 0.05$) for Model 1 and $r^2 = 0.97$ ($P < 0.05$) for Model 2. Predicted values correlated well with measured values for both models as determined by Bland-Altman analysis (figure 2). For Model 1, predicted values were overestimated by a mean value of 0.07 mg/L (range 1.08-1.89 mg/L), of which 92.3% of the total predicted values were within the limits of agreement. For Model 2, the predicted values were overestimated by a mean value of

0.12 mg/L (range 0.23-0.94 mg/L), of which 98.2% of the total predicted values were within the limits of agreement. Based on plausibility of the computed pharmacokinetic data as well as the better agreement between measured and predicted concentrations, Model 2 was chosen as final model.

Discussion

In this study we evaluated two published population pharmacokinetic models and subsequently developed a new population pharmacokinetic model for darunavir that better described our population and provided us the opportunity to estimate darunavir trough concentration and that therefore was considered preferable for routine use. We showed that darunavir concentrations from the validation set can be predicted with this population pharmacokinetic model with a mean overestimation of 0.12 mg/L (range 0.23-0.94 mg/L). The observed range could potentially be further narrowed by using more sophisticated pharmacokinetic software allowing the addition of other covariates. However, the developed model is sufficient for daily outpatient setting since 98.2% of the total predicted values were within the limits of agreement. The robustness of the developed population pharmacokinetic model was demonstrated with the dataset of hospital B using Passing-Bablok regression ($r^2 = 0.97$; $P < 0.05$). Consistent with the findings of Arab-Alameddine et al.,² a one-compartment model with first-order absorption and elimination resulted in the best fit when using our patient data. The selection of the final population pharmacokinetic model was not merely based on AIC but was also selected based on plausibility of the computed pharmacokinetic data as well as on the agreement between measured and predicted concentrations in the external validation. For the model with the best AIC (Model 1), both V_d and K_a were set on a fixed value, making that

submodel less dependent on patient factors such as body weight and more on literature values,² which did not seem logical. Therefore, the model with both CL_m and V_d set on Bayesian (Model 2), based on AIC in combination with the plausibility of the computed data, was chosen for external validation. In addition, the agreement between measured and predicted concentrations in the external validation (figures 1 and 2) was markedly better for Model 2 than for Model 1, and therefore Model 2 was chosen as final model.

The submodel with also K_a set on Bayesian resulted in a poorer fit, which could be due to the low number of darunavir samples drawn in the absorption phase; 0-4 h after drug intake.⁵ Further, a ratio of fat distribution (f_d) of 5 and the omission of f_r (fixed at a value of zero) provided better AIC scores. A possible explanation of a better fit with a fat distribution ratio of 5 might again be the relatively high lipophilicity of darunavir.²⁵ The improvement of the model with the omission of f_r is not a remarkable finding since darunavir is mainly eliminated by the liver (80%) and the renal elimination is negligible,²³ therefore, f_r appears not to be a significant covariate.

Due to the relative high lipophilicity of darunavir,²⁵ a two-compartment population pharmacokinetic model would be expected to demonstrate a better fit. However, the addition of a second compartment did not improve the fit. This suggests that there is insufficient information in the used dataset to parameterize a two-compartment model. This could be a result of suboptimal blood sampling time points post-administration, which is required for the estimation of parameters for a two-compartment model. Further, the estimation of parameters for a two-compartment model after extravascular administration with first-order absorption is difficult since the rate constants of distribution and absorption usually have the same order of magnitude and are therefore difficult to distinguish. In a real-life outpatient setting, biased

sampling may occur due to practical convenience. For the development of a two-compartment pharmacokinetic model, richer data is more convenient in contrast to the currently used scarce real-life outpatient data.

For the development and validation of this population pharmacokinetic model, observational datasets retrieved from standard care settings were utilized. The use of observational datasets has advantages compared to experimental datasets due to economic- and ethical reasons; although it can often include larger number of patients and minimize risks and discomfort for the patients, it also has drawbacks. The major disadvantages of observational datasets are missing data and inaccurate data due to documentation errors.²⁶ Despite these drawbacks, the use of observational datasets was preferred in relation to the aim of the present study. The population pharmacokinetic model was developed for utilization in a real-life HIV outpatient setting. Data retrieved from an experimental setting would lack the high inter-patient variability which is apparent in standard care. Furthermore, a study showed that relatively small errors (e.g. up to 25% of the being data erroneous) in data registration have negligible influence on population pharmacokinetic modelling,²⁶ which also justifies the use of observational datasets from two hospitals for the development of a population pharmacokinetic model and its validation. Larger errors could still have a significant effect on the population pharmacokinetic modelling process,²⁶ therefore, patients with undetectable darunavir concentrations (≤ 0.2 mg/L), or unknown weight, height, unknown time of drug intake or time of sample collection above the 10% cut off were excluded. Regarding the modelling approach utilized for this study, while nonlinear mixed effects modelling is a more standard approach for sparse PK data, ITSB was chosen for this study because it allows for using body weight and serum creatinine level as continuously changing covariates. Furthermore, this approach was successfully applied in earlier studies.^{27, 28}

The Bland-Altman analysis (figure 2) reveals that the relatively small observed overestimation of the current model primarily occurs in lower darunavir concentrations. One explanation could be the relatively high assay error at lower concentrations. Another explanation may be that overestimation at a lower concentration can be an indicator for multiple-compartment pharmacokinetics, due to saturation of peripheral compartments. Unfortunately, our data were not sufficiently informative for fitting to a two-compartment model as discussed before. A third explanation might be the occurrence of underlying confounders, such as food intake and pharmacogenomics, which are not included in the current model. An additional explanation could be the saturation of metabolism at higher concentrations resulting in a higher clearance at low concentrations than predicted. However, the overestimation is within the error of the assay and does not significantly influence the analytical results. Furthermore, 98.2% of the total predicted values were estimated within the limits of agreement, justifying the use of this model in daily practice.

In standard care, darunavir concentrations are measured when indicated¹⁴ and subsequently the time-adjusted darunavir trough concentrations can be predicted using the currently developed population pharmacokinetic model. The time-adjusted darunavir trough concentrations are subsequently dichotomized as either 'above' or 'below' cut-off values in accordance with the local treatment protocol.¹³ The used cut-off values do not represent the minimal effective concentrations but are used in standard care as cut-off values for follow-up. A darunavir trough concentration below 1.07 mg/L for the once-daily dosage or below 2.60 mg/L for the twice daily dosage is an indication for follow-up. This follow-up could consist of repeating the plasma drug concentration measurement on a new occasion, additional food intake advice and additional questions and guidance concerning therapy adherence.^{13, 14} In case a darunavir trough concentration is collected adequately in terms of sampling time, the

measured concentrations can be utilized directly according to the treatment protocol. However, outpatient setting blood collection is not performed at optimal time points in most cases due to practical reasons. In those cases, the population pharmacokinetic model developed in this study could provide the opportunity to translate the drug concentrations collected at suboptimal timepoints into trough concentrations. In order to investigate the pharmacokinetics of darunavir more in-depth and to investigate the potential contribution of other confounders to darunavir pharmacokinetics, denser pharmacokinetic sampling in combination with sophisticated software packages such as NONMEM (nonlinear mixed effect modelling) will be more suitable. However, that was not within the scope of the current study. In our opinion, TDM can be a useful tool for clinicians to optimize treatment especially when used in conjunction with disease related parameters such as viral load, CD4+ cell count, and clinical judgement.

A strength of the current study is that we used a large number of patient data from two different hospitals, one for the development and the other for the validation of the darunavir population pharmacokinetic model. Since the current aim is the utilization of the model in an outpatient setting, another strength is the use of data retrieved from the target population. A limitation of this study is that potentially non-adherent patient or patients with food intake problems were included, which may have introduced selection bias and increased variance. However, this was inevitable as these patients in particular are selected for TDM, since non-adherence or inadequate concomitant food intake are indications for TDM (bias by indication).¹⁴ Another limitation is the low number of blood samples in the absorption phase (0 – 4 h). Due to this gap of information, it was not possible to parameterize the absorption constant in the population pharmacokinetic model, leading to a fixed value based on literature.² Furthermore, the binding of darunavir to alpha 1-acid glycoprotein was not taken

into account in our model. However, the aim of this study was not to investigate the pharmacokinetics of darunavir in depth, for which, as aforementioned, a different approach and study design would have been required. This pharmacokinetic model developed and validated herein can pragmatically estimate darunavir trough concentrations in daily practice and will suffice to use in routine TDM.

Conclusion

A new one-compartment population pharmacokinetic model for darunavir was developed and externally validated. This model is robust and is applicable for TDM of darunavir in daily outpatient setting.

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Figure Legends

Figure 1. Passing – Bablok regression. The plot shows the agreement between C_{measured} and $C_{\text{predicted}}$, predicted with the population pharmacokinetic model (dashed lines, 95% confidence interval [CI]). A: Model 1, B: Model 2

Figure 2. Bland – Altman plot. The Bland-Altman plot shows the agreement between C_{measured} and $C_{\text{predicted}}$ estimated with the final population pharmacokinetic model. Mean of all: the mean concentration of C_{measured} and $C_{\text{predicted}}$. The dashed lines represent: Upper Limit of Agreement and Lower Limit of Agreement ($\pm 2 \times$ standard deviation). A: Model 1, B: Model 2

Table 1. Patient demographics hospitals A and B.

Characteristics	Hospital A (n=198)	Hospital B (n=170)
No. (%) of patients by sex		
Male	141 (71)	142 (84)
Female	57 (29)	28 (16)
Age (yr) ^a	54 (24-74)	52 (28-73)
Weight (kg) ^a	72.0 (40-123)	74.5 (41-120)
Height (cm) ^a	173.0 (150-193)	179.5 (151-202)
Body mass index (kg/m ²) ^a	24.6 (16.9-35.3)	24.0 (15.0-40.2)
Serum creatinine conc. (μmol/L) ^{a,b}	83.5 (44.2-230.7)	85.5 (36.0-329.0)
Dosage 800/100 once daily	162 (82)	144 (85)
Dosage 600/100 twice daily	36 (18)	26 (15)
Dose/mean wt (once-daily) (mg/kg) ^a	11.0 (6.5-20.0)	10.6 (6.6-19.5)
Dose/mean wt (twice-daily) (mg/kg) ^a	8.3 (4.9-15.0)	7.9 (5.0-14.6)
Tot. number of samples	198	170

^a Median (range); ^b During visit of drug level measurement ±15 days; n= number of participants; wt = weight

Table 2. Final population pharmacokinetic parameters.

Parameter	Model 1 AIC = 945.31		Model 2 AIC = 1584.89*	
	Mean (95% CI)	SD (95% CI)	Mean (95% CI)	SD (95% CI)
CL_m (L/h/70kgBW)	11.22 (9.54 – 13.38)	12.11 (8.39 – 16.59)	9.47 (8.24 – 10.65)	6.19 (4.85 – 7.76)
V_d (L/kgLBMc)	1.42	-	2.13 (1.39 – 3.26)	2.60 (1.43 – 4.66)
K_a (h⁻¹)^{a,c}	1.04	-	1.04	-
F^b	0.82	-	0.82	-
f_r	0	-	0	-
Fat distribution	5	-	5	-

^a Literature value (2); ^b Literature value from SPC(17); ^c set on fixed value; SD: standard deviation; (95% CI); 95% confidence interval; CL_m: metabolic clearance; V_d: volume of distribution; K_a: first order absorption constant; F: bioavailability; *chosen as final population pharmacokinetic model

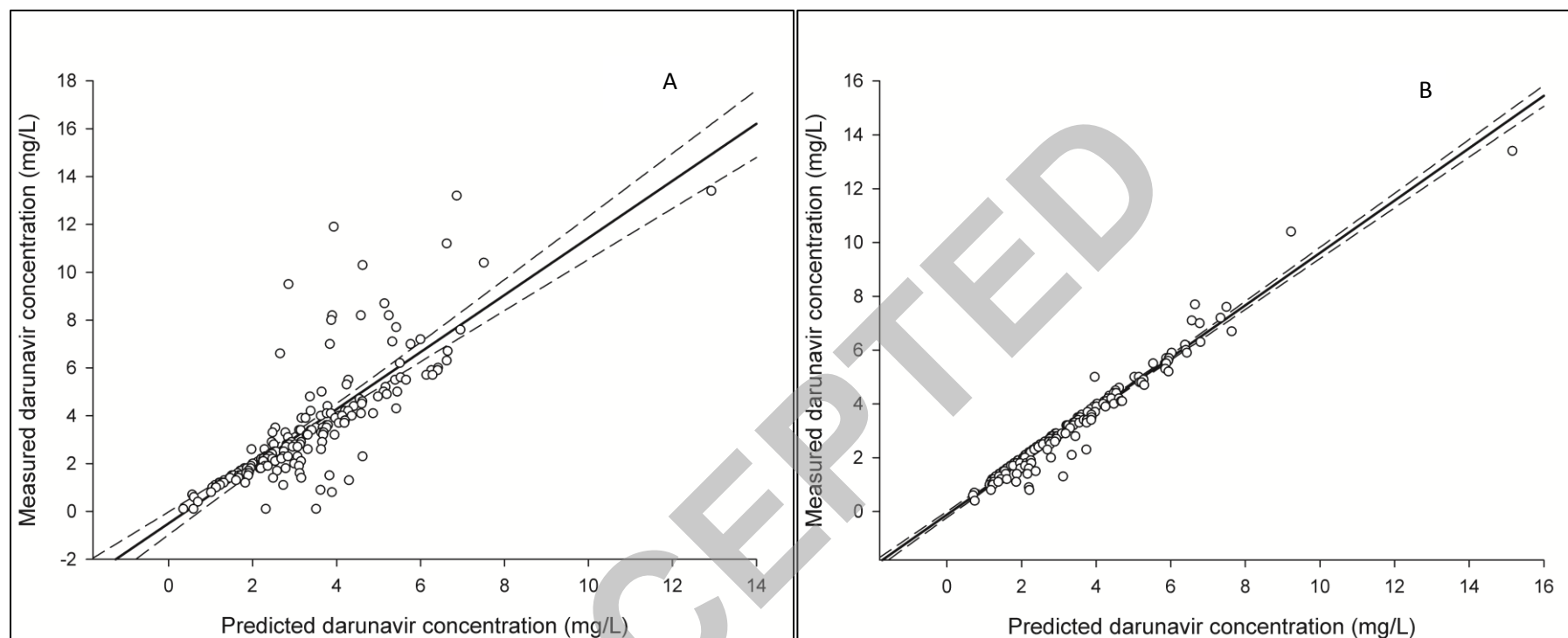


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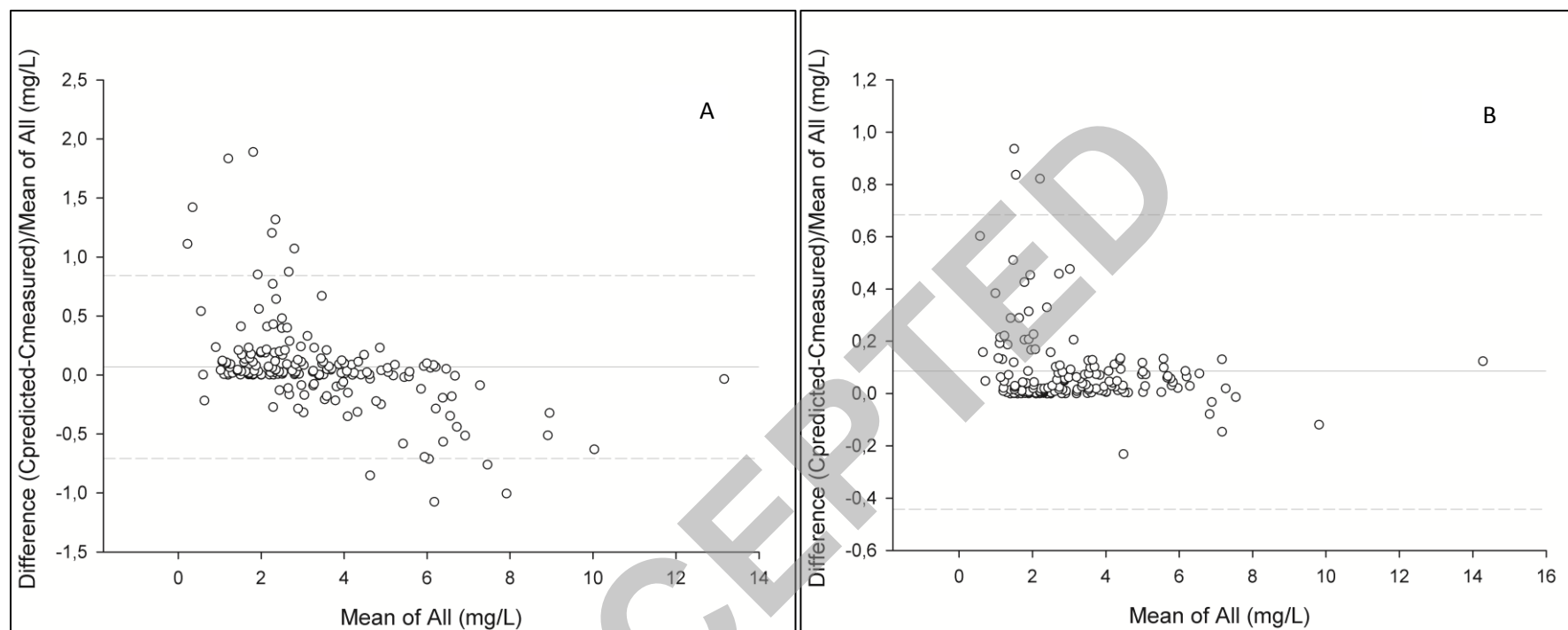


Figure 2. Bland – Altman plot. The Bland-Altman plot shows the agreement between C_{measured} and $C_{\text{predicted}}$ estimated with the final population pharmacokinetic model. Mean of all: the mean concentration of C_{measured} and $C_{\text{predicted}}$. The dashed lines represent: Upper Limit Of Agreement and Lower Limit Of Agreement ($\pm 2 \times$ standard deviation). A: Model 1, B: Model 2